



NDA 50-722/S-018
NDA 50-723/S-015
NDA 50-758/S-016
NDA 50-759/S-021

Hoffmann-La Roche, Inc.
Attention: Wendy L Corbett, Ph.D., MBA
Associate Director, Pharma Development Regulatory
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Corbett:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

NDA Number	Drug Product	Supplement Number	Date of Supplement	Date of Receipt
50-722	CellCept [®] (mycophenolate mofetil) Capsules, 250 mg	S-018	November 8, 2007	November 9, 2007
50-723	CellCept [®] (mycophenolate mofetil) Tablets, 500 mg	S-015	November 8, 2007	November 9, 2007
50-758	CellCept [®] (mycophenolate mofetil hydrochloride for injection) Intravenous, 500 mg/ 20 mL	S-016	November 8, 2007	November 9, 2007
50-759	CellCept [®] (mycophenolate mofetil for oral suspension) Oral Suspension, 200 mg/mL	S-021	November 8, 2007	November 9, 2007

These applications are subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We also acknowledge receipt of your submissions dated April 29, 2008.

These supplemental applications provides for revisions to the Package Insert as follows (~~strike through text~~ = deletions, underlined text = additions):

1. The **WARNINGS** section has been revised as follows:

WARNINGS

(see *boxed WARNING*)

Lymphoma and Malignancy

Patients receiving immunosuppressive regimens involving combinations of drugs, including CellCept, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see **ADVERSE REACTIONS**). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

~~Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis. In patients receiving CellCept (2 g or 3 g) in controlled studies for prevention of renal, cardiac or hepatic rejection, fatal infection/sepsis occurred in approximately 2% of renal and cardiac patients and in 5% of hepatic patients (see **ADVERSE REACTIONS**).~~

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving CellCept (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients (see **ADVERSE REACTIONS**).

In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed (see **ADVERSE REACTIONS**).

Combination with Other Immunosuppressive Agents

CellCept has been administered in combination with the following agents in clinical trials: antithymocyte globulin (ATGAM[®]), OKT3 (Orthoclone OKT[®] 3), cyclosporine (Sandimmune[®], Neoral[®]) and corticosteroids. The efficacy and safety of the use of CellCept in combination with other immunosuppressive agents have not been determined.

~~Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving CellCept (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients (see **ADVERSE REACTIONS**).~~

~~In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed (see **ADVERSE REACTIONS**).~~

Infections

Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis. In patients receiving CellCept (2 g or 3 g) in controlled studies for prevention of renal, cardiac or hepatic

rejection, fatal infection/sepsis occurred in approximately 2% of renal and cardiac patients and in 5% of hepatic patients (see **ADVERSE REACTIONS**).

Progressive Multifocal Leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with CellCept. Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. The reported cases generally had risk factors for PML, including treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

2. In the **ADVERSE REACTIONS** section, the first paragraph has been revised as follows:

ADVERSE REACTIONS

The principal adverse reactions associated with the administration of CellCept include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections eg, opportunistic infection (see **WARNINGS: Infections and WARNINGS: Progressive Multifocal Leukoencephalopathy (PML)**). The adverse event profile associated with the administration of CellCept Intravenous has been shown to be similar to that observed after administration of oral dosage forms of CellCept.

3. In the **ADVERSE REACTIONS** section, the 9th, 10th, 12th and the 13th paragraphs of the have been revised as follows:

Patients receiving CellCept alone or as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see **WARNINGS: Lymphoma and Malignancy**). The incidence of malignancies among the 1483 patients treated in controlled trials for the prevention of renal allograft rejection who were followed for ≥ 1 year was similar to the incidence reported in the literature for renal allograft recipients.

Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving CellCept (2 g or 3 g daily) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients followed for at least 1 year (see **WARNINGS: Lymphoma and Malignancy**). Non-melanoma skin carcinomas occurred in 1.6% to 4.2% of patients, other types of malignancy in 0.7% to 2.1% of patients. Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data.

Severe neutropenia ($ANC < 0.5 \times 10^3/\mu L$) developed in up to 2.0% of renal transplant patients, up to 2.8% of cardiac transplant patients and up to 3.6% of hepatic transplant patients receiving CellCept 3 g daily (see **WARNINGS: Neutropenia**, **PRECAUTIONS: Laboratory Tests** and **DOSAGE AND ADMINISTRATION**).

All transplant patients are at increased risk of opportunistic infections. The risk increases with total immunosuppressive load (see **WARNINGS: Infections** and **WARNINGS: Progressive Multifocal Leukoencephalopathy (PML)**). Table 9 shows the incidence of opportunistic infections that occurred in the renal, cardiac, and hepatic transplant populations in the azathioprine-controlled prevention trials:

4. In the **ADVERSE REACTIONS** section, the 16th paragraph has been revised as follows:

In patients receiving CellCept (2 g or 3 g) in controlled studies for prevention of renal, cardiac or hepatic rejection, fatal infection/sepsis occurred in approximately 2% of renal and cardiac patients and in 5% of hepatic patients (see **WARNINGS: Infections**).

5. The **ADVERSE REACTIONS/Postmarketing Experience** subsection has been revised as follows:

Postmarketing Experience

Congenital Disorders: Congenital malformations including ear malformations have been reported in offspring of patients exposed to mycophenolate mofetil during pregnancy (see **WARNINGS: Pregnancy**).

Digestive: Colitis (sometimes caused by cytomegalovirus), pancreatitis, isolated cases of intestinal villous atrophy.

Resistance Mechanism Disorders: Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infection. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with CellCept. The reported cases generally had risk factors for PML, including treatment with immunosuppressant therapies and impairment of immune function.

6. In the **DOSAGE AND ADMINISTRATION/Dosage Adjustments** subsection, the 3rd paragraph has been revised as follows:

If neutropenia develops ($ANC < 1.3 \times 10^3/\mu L$), dosing with CellCept should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see **WARNINGS: Neutropenia**, **ADVERSE REACTIONS**, and **PRECAUTIONS: Laboratory Tests**).

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We have completed our review of these applications, as amended and they are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Submit labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions “**SPL for approved supplements NDA 50-722/S-018, NDA 50-723/S-015, NDA 50-758/S-016, and NDA 50-759/S-021.**”

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Hyun Son, Pharm.D., Senior Regulatory Management Officer, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and
Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert

**This is a representation of an electronic record that was signed electronically and
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/s/

Renata Albrecht
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